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1. Current literature highlights

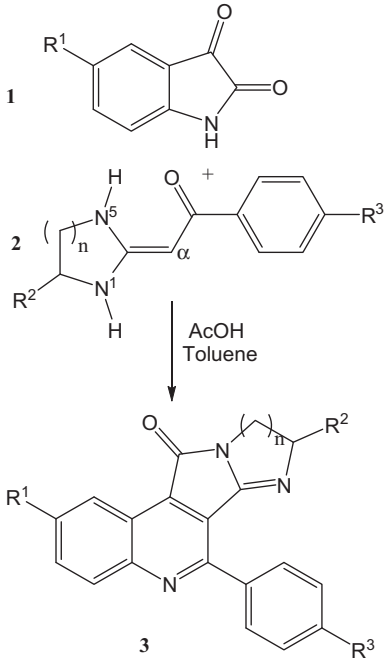
1.1. The cascade reaction of isatins with heterocyclic ketene aminals

Quinoline derivatives often have biological or pharmacological activity and thus are important molecules in drug discovery. Over the years, many methods have been developed to permit synthetic access, and the importance of these routes has been confirmed by the regular use of named reactions such as the Skraup, Doebner–von Miller, Friedländer, Pfitzinger, Conrad–Limpach and Combes syntheses. The biological and pharmacological properties of quinolines include anti-cancer, antituberculosis, antifungal, and anti-inflammatory activities, and many other compounds act as ligands for adenosine receptors, agonists of P-selectin and inhibitors of caspases.

However, the preparative approaches to these molecules are frequently multi-step, and there remains a need for concise and efficient approaches to quinoline synthesis. There has been a recent rapid growth in interest in one pot transformations, wherein complex molecular scaffolds can be readily built up through cascade chemistry, saving considerable synthetic time and effort. A recent publication describes the reaction of heterocyclic ketene acetals (HKAs) with isatins to generate novel imidazopyrroloquinoline derivatives in good to excellent yield.[1]

Within the HKAs (**2**), the conjugation of electron-donating amino groups and the electron-withdrawing carbonyl through a polarised double bond, results in high electron density on the α-carbon and the two secondary amino groups (N1 and N5). Thus they can act as bis-nucleophiles and react rapidly with bis-electrophiles such as isatins (**1**) to generate fused heterocyclic products (**3**).

The reaction to generate imidazopyrroloquinoline derivatives from 5-membered HKAs (**2**, $n = 1$) was investigated in a range of solvents employing various catalysts including zinc chloride and



trifluoroacetic acid. Ultimately it was found that the best yields were obtained using acetic acid in toluene under reflux for 4 h. A number of other five-membered HKAs were used as substrates to react with isatins, and then the reaction was also extended to six- (**2**, $n = 2$) and seven-membered (**2**, $n = 3$) HKAs, building a library of 27 variants. Overall, the compounds were produced in good to excellent yields with very high regioselectivity, using an efficient cascade reaction highly suitable for combinatorial synthesis.

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2. A summary of the papers in this month's issue

2.1. Solid-phase synthesis

A multistep approach to construct novel 3-(1*H*-benzo[*d*]imidazol-2-yl)imidazolidine-2,4-diones and 3-(1*H*-benzo[*d*]imidazol-2-yl)-2-thioxoimidazolidin-4-ones from commercially available amino acids, amines, and carboxylic acids has been described. The desired aminobenzimidazole tethered hydantoins or thiohydantoins were isolated in good yields.[2]

An efficient method for the solid-phase synthesis of hydroxamic acids has been described. The method comprises the nucleophilic displacement of esters immobilized on PEGA resins with hydroxylamine/sodium hydroxide in isopropanol. The hydroxyaminolysis protocol is compatible with a broad range of PEGA-supported peptide and peptidomimetic esters, and also found to be compatible with two new strategies for the synthesis of solid-supported lactams and diketopiperazines.[3]

A recent paper describes a convenient method for the direct amidation of methyl and ethyl β-ketoesters to generate solid-supported β-ketohydroxamates or β-ketoamides and the application of this methodology to the synthesis of 1,5-disubstituted pyrazole-4-hydroxamic acids and pyrazole-4-carboxamides.[4]

2.2. Solution-phase synthesis

A novel multicomponent assembly process-cycloaddition sequence has been applied to the facile synthesis of β-carboline intermediates to gain rapid access to novel derivatives of Yohimbine-like and Corynanthe-like compounds. These products may be easily diversified by cross-coupling reactions and *N*-derivatisations to generate small compound libraries.[5]

2.3. Scaffolds and synthons for combinatorial libraries

No papers this month.

2.4. Solid-phase supported reagents

The design and synthesis of a novel and selective SH-group biotinylating reagent, KSH-1, for the biotinylation of small molecules using solid-phase chemistry, has been described. The results demonstrate that this reagent efficiently biotinylated the small molecule, captopril, and afforded products in high yield and purity.[6]

Silica-supported boron trifluoride ($BF_3{\cdot}SiO_2$) has been used as an efficient and reusable catalyst for the synthesis of highly diversified tetrahydropyridines by one-pot multicomponent reactions of amines and aldehydes with β-ketoester. This method proceeds through the intermolecular Mannich reaction followed by intramolecular Mannich reaction. This method has the advantage of easy work-up, convenient, relatively short reaction times and the products were isolated with high yields.[7]

2.5. Novel resins, linkers and techniques

Fragment-based lead discovery is a drug discovery approach that has emerged in the past decade. Because the initial fragments identified in screening typically show weak binding affinity, an intensive medicinal chemistry effort would be required to grow initial fragments into a potential lead compound. A recent publication demonstrates a kinase focused evolved fragment (KFEF) library, constructed by click chemistry-based fragment assembly, that is a valuable source of kinase inhibitors. The screening of this triazole-based KFEF library allowed the rapid identification of potent lead candidates for FLT3 and GSK3β kinase.[8]

2.6. Library applications

Libraries of dibasic compounds designed around the molecular scaffold of the DA_2/β_2 dual agonist sibenadet (Viozan™) have yielded a number of promising starting points that have been further optimised into novel potent and selective target molecules with required pharmacokinetic properties. One compound was selected as a novel, high potency, and highly efficacious β_2-agonist with high selectivity and a duration of action commensurable with once daily dosing.[9]

A novel series of pyrrolidine derived BACE-1 inhibitors have been developed. The potency of the weak initial lead structure was enhanced using library-based SAR methods, and the series was further advanced by rational design while maintaining a minimal ligand binding efficiency threshold. Ultimately, the co-crystal structure was obtained revealing that these inhibitors interacted with the enzyme in a unique fashion and allowed for potent binding in a nontraditional fashion.[10]

A recent study has achieved the design and diversity-oriented synthesis of novel 1,4-thiazepine derivatives. These compounds are embedded with a carbazole, pyrazole or isoxazole motif via microwave-assisted multicomponent reactions under solvent-free condition. The compounds have been subjected to testing for *in vitro* antioxidant and cytotoxic activities, resulting in the finding that 1,4-thiazepine derivatives not only have significant antioxidant activity, but also exhibit remarkably selective cytotoxicity to carcinoma cell line HCT 116.[11]

Thirty-one 2′-hydroxychalcones have been prepared via solid-phase synthesis using base-catalysed aldol condensation of substituted 2′-hydroxyacetophenones and benzaldehydes. Chalcones were tested for their growth inhibitory activity in three human tumour cell lines (MCF-7, NCI-H460 and A375-C5) and results revealed that several of the tested compounds caused a pronounced dose-dependent growth inhibitory effect on the tumour cell lines.[12]

Naturally occurring peptides often possess a macrocyclic and *N*-methylated backbone. These features grant them structural rigidity, high affinity to targets, proteolytic resistance, and occasionally membrane permeability. Because such peptides are produced by either nonribosomal peptide synthetases or enzymatic post-translational modifications, it is a formidable challenge to prepare libraries to screen for bioactivity. A new means of synthesising a *de novo* library of "natural product-like" macrocyclic *N*-methyl-peptides has been described. The selection of anti-E6AP macrocyclic *N*-methyl-peptides, has resulted in the identification of one compound which strongly inhibits polyubiqutination of proteins such as p53.[13]

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